CHAPTER 31

Multiple myeloma and other plasma cell dyscrasias

Sundar Jagannath, MD, Paul Richardson, MD, and Nikhil C. Munshi, MD

MULTIPLE MYELOMA

Multiple myeloma is a disseminated malignancy of monoclonal plasma cells that accounts for 8% of all hematologic cancers. In the year 2005, an estimated 15,980 new cases will be diagnosed in the United States, and 11,300 Americans will die of this disease. Incidence rates for myeloma (5.3 in men and 3.5 in women) and mortality rates (3.7 in men and 2.5 in women) per 100,000 population have remained stable for the past decade.

Epidemiology

Gender Men are affected more frequently than women (1.4:1.0 ratio).

Age The median age at presentation is 71 years, according to most tumor registries, although the median age reported in studies is approximately 60 years.

Race The annual incidence per 100,000 population is 6.4 among white men and 4.1 among white women. Among black men and women, the frequency doubles to 12.7 and 10.0, respectively, per 100,000 population. This racial difference is not explained by socioeconomic or environmental factors and is presumably due to unknown genetic factors.

Geography There is no clear geographic distribution of multiple myeloma. In Europe, the highest rates are noted in the Nordic countries, the United Kingdom, Switzerland, and Israel. France, Germany, Austria, and Slovenia have a lower incidence, and developing countries have the lowest incidence. This higher relative incidence in more developed countries probably results from the combination of a longer life expectancy and more frequent medical surveillance.

Survival The 5-year survival rate for all patients treated with conventional therapy is approximately 25%-30%. The 5-year survival rate is lower among patients ≥ age 65 (20%-25%) than in those < age 65 (30%-35%).

Etiology and risk factors

No predisposing factors for the development of multiple myeloma have been confirmed.

Environment Some causative factors that have been suggested include radiation exposure (radiologists and radium dial workers), occupational exposure (agricultural, chemical, metallurgical, rubber plant, pulp and paper workers and leather tanners), and chemical exposure to formaldehyde, epichlorohydrin, Agent Orange, hair dyes, paint sprays, and asbestos. None of these associations has proven to be statistically significant, and all have been contradicted by negative correlations. The initial report that survivors of the atomic bombings in Japan had an increased risk of developing myeloma has been refuted by longer follow-up.

Viruses A preliminary report in a limited number of patients noted the presence of herpesvirus 8 in the dendritic cells in patients with multiple myeloma. However, further evaluation by a number of investigators has failed to confirm this result. Patients with myeloma also do not have immune response against this virus.

Cytogenetics Karyotypic abnormalities in myeloma are complex, with both numeric and structural abnormalities. DNA aneuploidy is observed in more than 90% of cases, predominantly hyperdiploid, and less than 10% have hypodiploidy, which carries a poor prognosis. Recurrent nonrandom structural abnormalities have been identified and linked to pathogenesis and prognosis of myeloma. The immunoglobulin heavy-chain gene at 14q32 is frequently involved in translocations with partner chromosomes 4, 6, 8, 11, and 16. The location and oncogenes involved are shown in Table 1. Translocations involving chromosome 4 and 16 and del17p13 (p53) have been associated with a poor prognosis. Del13q or monosomy 13 is observed in 15%-20% of patients with conventional cytogenetics and also carries a poor prognosis across standard and high-dose therapies. Interphase fluorescence in situ hybridization (FISH) with a specific probe for chromosome 13q34 (retinoblastoma gene, *Rb 1*) identifies this abnormality in up to 50% of patients, with a less clear prognosis implication.

Interactions between multiple myeloma (MM) cells and their microenvironment, the extracellular matrix and the bone marrow stromal cells (BMSCs), allow MM cells to survive, grow, migrate, and resist apoptosis induced by traditional chemotherapies. These effects are partially mediated through adhesion-mediated signalling and partly through various cytokines, including IL-6, VEGF, IGF-1, and IL-21. The molecular signals mediating the proliferative effects include the *ras/raf* MAPK pathway, whereas the P13-K/Akt pathway provides cell survival and drug resistance signals. Improved understanding of these interactions and the molecular mechanisms mediating them has now allowed us to evaluate novel therapies that directly target MM cells as well as act on the bone marrow microenvironment.

Genetic factors Although multiple myeloma is not an inherited disease, there have been numerous case reports of multiple incidence in the same family. However, a case-control study revealed no significant increase in the incidence among relatives of patients who had multiple myeloma, other hematologic malignancies, or other cancers.

TABLE 1: The location and oncogenes involved in multiple myeloma

Locus	Oncogene	Incidence
11q13	Cyclin D1	15%-20%
6p21	Cyclin D3	5%
4p16.3	FGFR3 and MMSET	12%
16q23	c-*maf*	5%-10%
8q24	c-*myc*	< 10%
6p25	MUM1/IRF4	5%
20q11	MAFB	5%
1q21-34	*bcl*-9, IL-6R, *mcl*-1	Frequent

Monoclonal gammopathy of unknown significance (MGUS) Patients with MGUS develop myeloma, macroglobulinemic lymphoma, or amyloidosis at a rate of 1% per year.

Signs and symptoms

The clinical features of multiple myeloma are variable. Findings that suggest the diagnosis include lytic bone lesions, anemia, azotemia, hypercalcemia, and recurrent infections. Approximately 30% of patients are free of symptoms and are diagnosed by chance.

Bone disease Bone pain, especially from compression fractures of the vertebrae or ribs, is the most common symptom. At diagnosis, 70% of patients have lytic lesions, which are due to accelerated bone resorption. These changes are induced by factors modulating osteoclast activity and produced by the bone marrow microenvironment and, to a lesser extent, myeloma cells. These factors include interleukin (IL)-1B, tumor necrosis factor (TNF)-α, and IL-6 as well as newly identified factors such as osteoprotogerin, TNF-related activation-induced cytokine (TRANCE), and receptor activator of nuclear factor kappa B (RANK) ligand. DKK-1 has been described as a soluble factor produced by multiple myeloma cells inhibiting osteoblastic activity.

Anemia A normocytic, normochromic anemia is present in 60% of patients at diagnosis. This is due primarily to the decreased production of RBCs by marrow, infiltration with plasma cells, and the suppressive effect of various cytokines. Patients with renal failure may also have decreased levels of erythropoietin, which may worsen the degree of anemia.

Hypercalcemia Among newly diagnosed patients, 20% have hypercalcemia (corrected serum calcium level, > 11.5 mg/dL) secondary to progressive bone

TABLE 2: Common laboratory features of plasma cell dyscrasias

Multiple myeloma
Marrow plasmacytosis > 10%
Monoclonal immunoglobulin peak (usually > 3.0 g/dL)
Clonal plasma cells
Presence of Bence Jones protein
Lytic bone lesions or diffuse osteopenia
Related organ or tissue impairment
Smoldering myeloma
Same as multiple myeloma but without symptoms and;
Hemoglobin > 10.5 g/dL
Monoclonal immunoglobulin peak (< 4.5 g/dL)
Normal serum calcium and creatinine levels
No lytic bone lesions
Solitary plasmacytoma of bone (SPB)
Solitary bone lesion due to plasma cell tumor
Normal skeletal survey and MRI of the skull, spine, and pelvis
Normal bone marrow plasmacytosis
No anemia, hypercalcemia, or renal disease
Preserved levels of uninvolved immunoglobulins
Monoclonal gammopathy of unknown significance (MGUS)
Monoclonal immunoglobulin level < 3.0 g/dL
Bone marrow plasma cells < 10%
No bone lesions
No symptoms due to plasma cell dyscrasia
Usually preserved levels of uninvolved immunoglobulins
No related organ or tissue impairment
Amyloidosis without myeloma
Same as MGUS plus evidence of amyloidosis on biopsy

destruction, which may be exacerbated by prolonged immobility. Hypercalcemia should be suspected in patients with myeloma who have nausea, fatigue, confusion, polyuria, or constipation. It may suggest high tumor burden. It should be considered an oncologic emergency and promptly treated.

Renal failure Approximately 20% of patients present with renal insufficiency and another 20% develop this complication in later phases of the disease. Light-chain cast nephropathy is the most common cause of renal failure. Additional causes include hypercalcemia, dehydration, and hyperuricemia. Uncommonly, amyloidosis, light-chain deposition disease, nonsteroidal anti-inflammatory agents taken for pain control, intravenous radiographic contrast administration, and calcium stones may contribute to renal failure. More recently, bisphosphonate therapy has been associated with renal failure.

Infections Many patients with myeloma develop bacterial infections that may be serious. In the past, gram-positive organisms (eg, *Streptococcus pneumoniae,*

Staphylococcus aureus) and *Haemophilus influenzae* were the most common pathogens. More recently, however, gram-negative organisms have become frequent. The increased susceptibility of patients with myeloma to bacterial infections, specifically with encapsulated organisms, has been attributed to impairments of host-defense mechanisms, such as hypogammaglobulinemia, granulocytopenia, and decreased cell-mediated immunity.

Screening and diagnosis

No screening measures for multiple myeloma have demonstrated any benefit.

The diagnosis usually requires the presence of bone marrow plasmacytosis and a monoclonal protein in the urine and/or serum (Table 2). One immunoglobulin class is produced in excess, whereas the other immunoglobulin classes are usually depressed.

Initial work-up The initial work-up for patients suspected of having a plasma cell dyscrasia should include:

- CBC with differential count and platelet count
- routine serum chemistry panel (eg, calcium, BUN, creatinine)
- bone marrow aspirate and biopsy to assess plasmacytosis
- serum protein electrophoresis and immunofixation to define protein type
- 24-hour urine protein, electrophoresis, and immunofixation
- quantitative immunoglobulin levels
- skeletal survey (bone scans contribute little since isotope uptake is often low in purely lytic bone disease)
- cytogenetics.

The recently available serum free light chain assay is useful in patients with light chain-only disease, oligo- or nonsecretory myeloma, renal failure, and amyloidosis.

MRI is an excellent tool for evaluation of spinal cord compression/impingement. In addition, MRI identifies generalized signal abnormalities and focal lesions that can be monitored after therapy. MRI is especially useful in staging nonsecretory disease presenting as macrofocal lesions.

In addition, prognostic factors, such as β_2-microglobulin (β2M), C-reactive protein, lactic dehydrogenase (LDH) levels, plasma cell-labeling index, and ploidy, may provide useful data.

Laboratory and pathologic features

Peripheral blood The peripheral blood smear may reveal a normocytic, normochromic anemia with rouleaux formation. Plasma cells may also be seen.

Bone marrow Bone marrow examination usually reveals an increased number of plasma cells (> 15%). These cells are strongly positive for CD38, CD138, and

TABLE 3: Durie-Salmon staging system for multiple myeloma

Stage	Criteria	Myeloma cell mass ($\times 10^{12}$ cells/m^2)
I	Hemoglobin > 10 g/dL	< 0.6 (low)
	Serum calcium level ≤12 mg/dL (normal)	
	Normal bone or solitary plasmacytoma on x-ray	
	Low M-component production rate:	
	IgG < 5 g/dL	
	IgA < 3 g/dL	
	Bence Jones protein < 4 g/24 h	
II	Not fitting stage I or III	0.6-1.2 (intermediate)
III	Hemoglobin < 8.5 g/dL	> 1.2 (high)
	Serum calcium level > 12 mg/dL	
	Multiple lytic bone lesions on x-ray	
	High M-component production rate:	
	IgG > 7 g/dL	
	IgA > 5 g/dL	
	Bence Jones protein > 12 g/24 h	

Subclassification	Criterion
A	Normal renal function (serum creatinine level < 2.0 mg/dL)
B	Abnormal renal function (serum creatinine level ≥ 2.0 mg/dL)

cytoplasmic immunoglobulin (cIg) and are negative for CD5, CD20, and surface immunoglobulin (sIg) expression. Whereas normal plasma cells express CD19, malignant plasma cells lose its expression, and this may be related to the loss of *Pax-5* gene expression. CD10 expression is generally negative but has sometimes been noted in advanced disease. Monoclonality may be demonstrated by immunoperoxidase staining with κ and λ antibodies.

The pattern of bone marrow involvement in plasma cell myeloma may be macrofocal. As a result, plasma cell count may be normal when an aspirate misses the focal aggregates of plasma cells that are better visualized radiographically or on direct needle biopsy.

Monoclonal proteins The types of monoclonal protein produced are IgG (60%), IgA (20%), IgD (2%), IgE (< 0.1%), or light-chain κ or λ only (18%). Biclonal elevations of myeloma proteins occur in < 1% of patients, and < 5% of patients are considered to have nonsecretory disease because their plasma cells do not secrete detectable levels of monoclonal immunoglobulin.

Staging and prognosis

The Durie-Salmon staging system is employed most frequently to stage multiple myeloma (Table 3). However, the variability in interpretation of staging criteria has resulted, in part, from imprecise quantification of the extent of bone lesions and from factors other than myeloma that contribute to hypercalcemia (eg, immobility) or anemia (eg, renal failure). Additionally, this staging system has not been predictive of response or survival in the studies using high-dose therapy or novel agents.

Prognosis

Cytogenetic abnormalities Chromosomal abnormalities, especially loss of whole chromosome 13 (monosomy) or deletions of parts of chromosome 13 (13q), with hypodiploid have been associated with inferior survival after both standard chemotherapy and high-dose therapy. Primary translocations involve 11q13 (cyclin D1), 6p21 (cyclin D3), 4p16 (FGFR3), and 16q23 (c-*maf*). Multivariate analysis has shown these chromosomal changes to be the most important predictors of survival.

β2M Serum β2M level is an important and convenient prognostic indicator. When cytogenetic changes are not studied, β2M is consistently the most important prognostic indicator on multivariate analysis. As β2M is excreted by the kidneys, high levels are observed in patients with renal failure; in this setting, the interpretation of an elevated value is unclear.

LDH High LDH levels also have been associated with plasmablastic disease, extramedullary tumor, plasma cell leukemia, plasma cell hypodiploidy, drug resistance, and shortened survival.

Other indicators of shortened survival include elevated C-reactive protein, DNA hypodiploidy, high plasma cell-labeling indices, and plasmablastic histology. Patients with DNA hypodiploidy are also less likely to respond to chemotherapy.

Treatment response criteria

Since the criteria for treatment response among patients with multiple myeloma have varied among institutions, response rates have been difficult to compare in the past. Bence Jones protein is reduced more rapidly in responders than is serum myeloma protein because of the rapid renal catabolism of light chains.

The criteria for partial response are:

- > 50% reduction in serum myeloma protein
- > 90% reduction in Bence Jones protein.

Criteria for complete response include:

- disappearance of serum myeloma protein and Bence Jones protein by immunofixation
- < 5% plasma cells in bone marow.

TABLE 4: Proposed standard treatment of multiple myeloma

Disease or patient status	Treatment approach
Initial therapy	
Candidates for high-dose therapy	
Dexamethasone	40 mg on days 1-4, 9-12, and 17-20 every 35 days or on days 1-4 every 2 weeks
Dexamethasone/thalidomide	Dexamethasone as above with thalidomide (200 mg/d)
VAD	Vincristine (0.5 mg/d IV) + Adriamycin ($10\ mg/m^2$/d IV), both given as continuous infusion on days 1-4, along with dexamethasone (40 mg) on days 1-4, 9-12, and 17-20 every 35 days
High-dose melphalan and SCT following induction therapy	
Noncandidates for high-dose therapy	
Above options or MP	Melphalan ($8\ mg/m^2$/d PO) + prednisone (100 mg/d PO) on days 1-4 every 4-5 weeks
Relapsed myeloma	
Conventional chemotherapy	Dexamethasone and thalidomide Alkylating-agent combination (MP, VBMCP) Cyclophosphamide, etoposide, DCEP
High-dose chemotherapy	Melphalan ($200\ mg/m^2$) and autotransplant mini-allogeneic transplant
Novel agents	Bortezomib ($1.3\ mg/m^2$) on days 1, 4, 8, and 11 every 3 weeks Melphalan, arsenic trioxide, ascorbic acid (MAC)
Clinical trials	Lenalidomide (phase II trials)

DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; SCT = stem-cell transplantation; VBMCP = vincristine, BiCNU, melphalan, cyclophosphamide, prednisone

Treatment

Exciting advances in the understanding of tumor biology and microenvironment–and their potential interaction–have helped to identify unique targets for rational therapeutic intervention to enhance outcome, which has not improved with conventional chemotherapy over the past 3 decades. Only 5%-10% of patients with multiple myeloma live longer than 10 years, and cure remains elusive.

NEWLY DIAGNOSED PATIENTS

Chemotherapy

Dexamethasone/thalidomide Thalidomide (Thalomid) has been employed alone and in combination with dexamethasone as initial therapy in newly diagnosed patients. When employed alone, response (50% reduction in paraprotein) was observed in 36% of patients; when it was used along with dexamethasone, the response rate was higher (72% and 64% in two studies), including a 16% complete response rate in one study. The results of a randomized Eastern Cooperative Oncology Group (ECOG) trial showed that the combination of thalidomide and dexamethasone was superior to dexamethasone alone (59% vs 41%, $P = .001$) and comparable to those with VAD (vincristine, Adriamycin [doxorubicin], and dexamethasone). This combination does not damage stem cells and allows adequate stem cell collection. A definite increase in thrombotic episodes has been observed with this combination, prompting prophylactic administration of coumadin or low molecular weight heparin.

VAD or VDD (vincristine, liposomal doxorubicin [Doxil], and dexamethasone) regimens spare stem cells and do not impair stem cell collection (Table 4). Such regimens produced a response rate of 55% in untreated patients, without improvement in overall survival over MP (melphalan [Alkeran] and prednisone). Responses occurred more rapidly with VAD-based regimens than with MP; these rapid responses provide an advantage in patients with hypercalcemia, renal failure, or severe bone pain. No dosage adjustment is necessary for renal failure. Use of this combination has decreased since the introduction of dexamethasone/thalidomide due to the need for a central line, the inconvenience of IV administration, and attendant toxicities.

Pulse dexamethasone alone has also been used in older patients and patients who need vertebral radiotherapy for spinal cord compression or for painful vertebral compressions that require immediate irradiation, as this approach avoids severe myelosuppression (Table 4).

MP The combination of melphalan and prednisone has been used over the past 30 years, and other combinations of multiple alkylating agents have not been found to be superior to MP. A meta-analysis of 18 published randomized trials comparing MP with other combination regimens arrived at the same conclusion. Combination chemotherapy is probably not superior to MP, even in poor-risk patients (Table 4). Approximately 40% of patients have responded to the MP regimen, with a median remission duration of 18 months and an overall median survival of 3 years.

MP and thalidomide (MPT) In a prospective, randomized trial in patients older than age 60, MPT produced an overall response rate of 78%, including a 28% rate of near complete response, compared with a near complete response rate of 5% with MP. MPT offers a possible alternative for older people who generally are not candidates for high-dose therapy.

Melphalan and other alkylating agents damage bone marrow stem cells, affecting ability to mobilize an adequate number of cells for high dose-therapy.

Extensive use of alkylating agents may also predispose patients to the subsequent development of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). These limitations have now substantially reduced the use of MP in newly diagnosed patients.

High-dose therapy following induction

High-dose therapy employed after induction therapy improves the response rate as well as event-free and overall survival. The impressive improvement in event-free survival (median, 28 vs 18 months) and overall survival (57 vs 42 months) reported in a randomized trial (IFM 90) has been confirmed by another large randomized trial (median overall survival, 54.8 vs 42.3 months) (MRC VII). Most of these studies enrolled patients < 65 years old. Older individuals (< age 70) tolerate high-dose therapy with peripheral stem cell support well, without excess mortality. Moreover, outcome, in terms of event-free and overall survival, is comparable to that in matched cohorts < 65 years old, making older individuals (≥ 65 years old) also candidates for high-dose therapy. More recently, older patients (> age 70) receiving intermediate-dose melphalan (100 mg/m^2) with stem cell support have been shown to have a better outcome than matched controls receiving conventional therapy.

A high-dose alkylating agent, most commonly melphalan at 200 mg/m^2 with peripheral blood stem cell support, is a standard conditioning regimen. Addition of total-body irradiation (TBI) does not improve the outcome but increases morbidity and results in occasional mortality. Interestingly, in a randomized study, Fermand et al have confirmed an equivalent survival benefit between up-front high-dose therapy vs high-dose therapy as salvage regimen at relapse following initial induction therapy.

Tandem transplants Improved outcome reported after tandem transplants in large cohorts of patients in single-institution studies has been confirmed in a mature randomized study. Seven years after initiation of therapy, the event-free survival (42% vs 21%) and overall survival (20% vs 10%) were superior for patients receiving tandem transplants (IFM 94). Another randomized trial with a shorter follow-up has confirmed the superior event-free survival (median, 34 vs 25 months) for patients receiving tandem transplants. The added benefit of the second transplant was not seen in a subset of patients with a complete response or a very good partial response (> 90% paraprotein reduction) after the first transplant.

Radiotherapy

Higher doses of radiotherapy (40-50 Gy) are employed for local control and cure of solitary plasmacytoma involving bone and extramedullary sites. Lower doses (20-30 Gy) may be employed for palliation of local bone pain from tumor infiltration, pathologic fractures, and spinal cord compression. It should be emphasized that excellent pain relief may be obtained by prompt institution of high-dose corticosteroid therapy, especially in newly diagnosed patients.

Radiotherapy should be employed sparingly, as irradiation of multiple sites may impair stem cell mobilization in patients who are candidates for high-dose

therapy. Employment of high doses of radiation to the spine may preclude the subsequent use of TBI as a conditioning regimen for high-dose therapy.

REMISSION MAINTENANCE

Alkylating agents

Maintenance therapy with alkylating agents has not prolonged survival, compared with no maintenance therapy. This approach is no longer recommended.

Steroids for maintenance Two large randomized trials have shown glucocorticoid maintenance prolongs the duration of remission and life expectancy. The first trial by the Southwest Oncology Group (SWOG) used prednisone (50 mg) every other day, whereas the maintenance regimen in the NCI-Canada trial contained dexamethasone (40 mg) daily for 4 days every 4 weeks.

Thalidomide Patients responding to thalidomide and achieving maximal response have received lower dose thalidomide (50-100 mg) with or without added dexamethasone (40 mg for 4 days every month) as maintenance therapy. In the MPT regimen, continued administration of thalidomide prolongs the duration of remission.

α-Interferon has been investigated as maintenance after conventional chemotherapy. A large overview of 24 randomized trials revealed a marginal improvement in median disease progression-free survival and overall survival durations of 6 months and 4 months, respectively. This minimal benefit is attained at significant cost and toxicity. A large, randomized intergroup trial has reported no benefit of interferon maintenance therapy (after conventional therapy and autotransplantation).

REFRACTORY OR RELAPSING DISEASE

Approximately 10%-30% of patients with newly diagnosed multiple myeloma are unresponsive to chemotherapy. Moreover, in virtually all patients who respond initially, the myeloma will relapse. Of patients who relapse after an unmaintained remission, approximately 60% achieve a second remission or stable disease with resumption of the original therapy.

Conventional chemotherapy

Alkylating agents, alone or in combination, have been effective in approximately one-third of patients with VAD-refractory disease. IV melphalan (70-100 mg/m^2) and the combination of high-dose cyclophosphamide (Cytoxan, Neosar) and etoposide are two examples of such regimens (Table 4).

Thalidomide has an established role in therapy for refractory/relapsed multiple myeloma, with 30% of patients achieving at least 50% reduction in paraprotein levels. Remissions obtained are durable: In a large cohort of patients with multiple myeloma receiving thalidomide, 2-year event-free survival rates of ~25% have been observed. Initially, thalidomide was employed in a dose-escalating schedule, starting at 200 mg and achieving a maximal dose of 800 mg. Recently, smaller doses have been employed in combination with steroids (Table 4).

TABLE 5: Supportive therapies for multiple myeloma

Problem	Therapy
Chronic anemia (especially with renal impairment)	Erythropoietin
Prolonged neutropenia with infection	G-CSF
Recurrent infections with IgG < 400 mg/dL	Gamma globulin
Osteoporosis	Bisphosphonates

G-CSF = granulocyte colony-stimulating factor

High-dose chemotherapy High-dose melphalan and stem cell rescue should be offered to patients who have deferred the transplant initially. A randomized trial on early vs late transplantation has shown that a survival benefit is conferred on the patients undergoing transplantation.

Novel agents

Lenalidomide (Revlimid, also known as CC-5013) is a small molecule, thalidomide analog with immunomodulatory effects. It has greater potency than thalidomide in preclinical studies and is better tolerated, with no neurotoxicity, somnolence or constipation. In a phase II trial, lenalidomide (30 mg daily for 3 weeks on and 1 week off) induced minimal responses or better in 37% of patients with relapsed or refractory myeloma. The addition of dexamathasone increased the overall response rate to 58% among the 91 patients treated on this trial.

Proteasome inhibition Bortezomib (Velcade, PS-341) is a first-in-class, potent, selective, and reversible small molecule inhibitor of the proteasome. The proteasome plays a key role in the degradation of ubiquinated proteins, which in turn have important functions in controlling tumor cell growth and survival both in vitro and in vivo.

A large multi-institution phase II trial of bortezomib (given IV at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 every 21 days) demonstrated remarkable activity in a heavily treated, relapsed and refractory patient population, including patients in whom transplantation failed and patients not responding to thalidomide, with durable responses in about 35% receiving bortezomib alone (with a number of complete responses). Side effects related to the drug were predominantly GI in nature, with neuropathy, fatigue, and reversible cytopenias also noted. Toxicities were generally manageable with supportive care and dose reduction. Patients who did not respond to bortezomib monotherapy (progressive disease after two cycles or stable disease after the first four cycles) were permitted to receive combination bortezomib and dexamethasone. Combination therapy induced additional responses in 18% of patients (13 of 74). The results of a large, randomized phase III trial of bortezomib compared with dexamethasone that enrolled 669 patients with relapsed multiple myeloma were recently reported at the 2004 annual meeting of the American Society of Clinical Oncology.

At the time of the interim analysis, significant improvement (58%) in median time to disease progression was observed with bortezomib compared with dexamethasone (5.7 vs 3.6 months, respectively; $P < .0001$). The most commonly reported adverse events for bortezomib at the interim analysis were gastrointestinal events, fatigue, pyrexia, and thrombocytopenia; for dexamethasone, they were fatigue, insomnia, and anemia.

Clinical studies are ongoing with bortezomib in combination with pegylated liposomal doxorubicin, thalidomide, melphalan, and lenalidomide, with better disease control in refractory myeloma. In patients with relapsed or refractory multiple myeloma, the objective response rate for bortezomib plus pegylated liposomal doxorubicin (30 mg/m^2 on day 4) in a phase I dose-escalation study was 77%. When bortezomib (1.0 or 1.3 mg/m^2) was administered with thalidomide (in doses ranging from 50 to 200 mg starting at cycle two), 58% of patients with relapsed or refractory disease achieved a complete or partial response. A phase I trial combining bortezomib with lenalidomide is now under way and promises less neuropathy than that seen with thalidomide.

Arsenic trioxide (Trisenox), administered as a daily IV infusion dosed at 0.15 mg/kg in a phase II study, has shown response in 3 of 14 relapsed refractory patients. Adverse effects included cytopenia requiring G-CSF (granulocyte colony-stimulating factor, filgrastim, Neupogen) support. Based on preclinical data suggesting synergism among arsenic trioxide, dexamethasone, and ascorbic acid, a phase II evaluation of this combination is in progress.

Allogeneic transplantation For younger patients with resistant relapse or with poor-prognosis disease (ie, deletion of chromosome 13), allogeneic transplantation may be an important option. However, high treatment-related mortality (30%-50%) with myeloablative allogeneic transplantation has discouraged the use of allografts in early-phase myeloma. New nonmyeloablative transplantation procedures that reduce mortality and exploit a graft-vs-tumor effect are being studied. In one study, 34 patients, including patients with relapsed or refractory disease, received melphalan at 200 mg/m^2 with autografting and then (40-120 days later) received allograft after nonmyeloablative conditioning. Treatment-related mortality at day 100 was 6%, with 53% of the patients achieving complete response. With a median follow-up of 328 days after allografting, the overall survival rate was 81%.

Supportive therapies

Various supportive therapies may be beneficial in patients with multiple myeloma (Table 5).

Chronic anemia Patients with chronic symptomatic anemia may benefit from a trial of epoetin alfa (Epogen, Procrit), 40,000 U given by SC injection once weekly. Darbepoetin alfa (Aranesp), dosed at 200 to 300 μg by SC injection every 2 to 3 weeks, is an alternative approach.

Infection Serious infection with encapsulated organisms is encountered by patients with myeloma due to their inability to mount successful antibody production (and lack of opsonization). Prompt institution of antibiotics is therefore

recommended in the face of systemic infection. Antibiotic prophylaxis is also recommended whenever high-dose glucocorticoids are used for treatment. Patients with recurrent serious infections may benefit from monthly gamma globulin. Shingles is not uncommon in these patients, and prophylaxis following transplantation and during bortezomib therapy is advised.

Bone pain or imminent fracture Therapy with bisphosphonates, such as pamidronate (Aredia), alendronate (Fosamax), or zoledronic acid (Zometa), may prevent or delay bone pain or recurrent or imminent pathologic fractures in patients with stage III disease and at least one bone lesion. Pamidronate administered over the long term (21 monthly treatments) to patients with stage III multiple myeloma with at least one lytic lesion has been shown to reduce skeletal events and decrease the need for irradiation. Moreover, patients without lytic lesions also show a decrease in bone mineral density, and this decrease persists despite chemotherapy. These patients may also benefit from therapy with pamidronate. Several clinical and preclinical studies suggest that pamidronate may have an antimyeloma effect.

Zoledronic acid, a more potent bisphosphonate, has comparable efficacy and safety to pamidronate in treatment of skeletal lesions. The ease of administration of a 4-mg dose, which reduces the infusion time to 15 minutes compared with 2 hours for pamidronate, has led to approval of zoledronic acid by the FDA for prevention of bone-related complications in myeloma. Caution should be exercised with long-term use of bisphosphonates, as renal impairment and osteonecrosis of the jaw bones have been reported.

Percutaneous vertebroplasty provides pain relief that is not only rapid but sustained, and it also strengthens the vertebral bodies. This procedure consists of injection of polymethyl methacrylate, the principal component of bone cement, in the vertebral body. It is performed with the patient under general or local anesthesia. Transient worsening of pain and fever may occur and is responsive to nonsteroidal anti-inflammatory agents.

Smoldering myeloma

Smoldering myeloma is a plasma cell dyscrasia where the disease is asymptomatic and is diagnosed by the chance finding of an elevated serum protein concentration during a screening examination.

Laboratory features Features of low tumor mass are usually present, without renal disease, hypercalcemia, or lytic bone lesions (Table 2). Marrow plasma cytosis occurs in less than 30% of patients, and anemia, if present, is mild (hemoglobin value > 10.5 g/dL).

Treatment Chemotherapy should be withheld until there is clear disease progression or a risk of a complication. The role of bisphosphonates is under investigation.

Prognostic factors Recent studies have helped define prognostic criteria for groups at high risk of early disease progression (eg, cytogenetic changes [especially chromosome 13], labeling index of plasma cells [> 0.4%], β2M levels

[4 mg/L], and diffuse disease activity or multiple focal lesions on MRI evaluation). Such criteria, along with the presence of lytic lesions, serum myeloma protein > 5 g/dL, and Bence Jones protein > 500 mg/24 h, identify patients at high risk of disease progression, in whom the early commencement of chemotherapy may be beneficial.

OTHER PLASMA CELL DYSCRASIAS

Other plasma cell dyscrasias include MGUS, solitary plasmacytoma of bone (SPB), solitary extramedullary plasmacytoma, Waldenström's macroglobulinemia, amyloidosis, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, and heavy-chain diseases.

Monoclonal gammopathy of unknown significance

MGUS occurs in 1% of normal individuals > 40 years old, and its frequency rises progressively with age.

Laboratory features Common laboratory features of MGUS are listed in Table 2.

Treatment Approximately 25% of patients with this disorder develop multiple myeloma, macroglobulinemia, or non-Hodgkin's lymphoma over 20 years. The initial concentration of serum monoclonal protein is a significant predictor of disease progression at 20 years. The long period of stability supports the value of annual monitoring with serum electrophoresis and blood counts and suggests that chemotherapy may be withheld until there is evidence of a serious disorder.

Solitary plasmacytoma of bone

Approximately 3% of patients with myeloma have SPB.

Laboratory features All patients have either no myeloma protein or very low levels in serum or urine (Table 2). MRI may reveal abnormalities not detected by bone survey and may upstage patients to multiple myeloma. Persistence of monoclonal protein for more than 1 year after irradiation predicts early progression to multiple myeloma.

Treatment for SPB consists of radiation therapy (at least 45 Gy). Multiple myeloma becomes evident in most patients over time, so that only 20% of patients remain free of disease for more than 10 years. The median time for disease progression is 2 years.

Solitary extramedullary plasmacytoma

In contrast to SPB, solitary extramedullary plasmacytoma is often truly localized and can be cured in most patients with localized radiation therapy (45-50 Gy) and/or resection.

Waldenström's macroglobulinemia

This uncommon disease is characterized by lymphoplasmacytic bone marrow and tissue infiltrate in addition to elevated IgM production. The mutation pattern analysis suggests that final transformation occurs in the postgerminal center IgM memory B cell. Corresponding with variation in cell morphology, there is variation in immunophenotype. Mature plasma cells exhibit CD38 antigen; however, lymphoid cells are typically CD19, CD20, CD22, and fmc7 positive.

Waldenström's macroglobulinemia usually affects people in the fifth to seventh decades of life and can cause symptoms due to tumor infiltration (marrow, lymph nodes, and/or spleen), circulating IgM (hyperviscosity, cryoglobulinemia, and/or cold agglutinin hemolytic anemia), and tissue deposition of IgM (neuropathy, glomerular disease, and/or amyloidosis).

Hyperviscosity syndrome With hyperviscosity syndrome, patients may have visual symptoms, dizziness, cardiopulmonary symptoms, decreased consciousness, and a bleeding diathesis. Neuropathy is usually due to an IgM antibody reacting with a myelin-associated glycoprotein (MAG).

Therapy for hyperviscosity consists of plasmapheresis followed by chemotherapy to control the malignant proliferation. Patients with poor performance status and elderly patients unable to tolerate chemotherapy may be maintained with periodic plasmapheresis.

Treatment Alkylating agents in combination with steroids or purine analogs remain the mainstay of therapy. Alkylating agents alone or in combination with steroids effect a 50% reduction in paraprotein in about half the patients, and the median survival is around 5 years. The purine analogs fludarabine (Fludara) and 2-CdA (cladribine) elicit a more rapid response than other agents, with a response rate of more than 75% observed in small series of patients. Preliminary results of a large, American multi-institution evaluation of fludarabine reported partial responses in only 33% of patients.

Purine analog therapy may result in significant myelosuppression in later cycles of therapy and prolonged immunosuppression with increased opportunistic infections. Purine analogs are effective salvage options in patients refractory to or relapsing following alkylator therapy. Patients refractory to one purine analog are rarely salvaged by a different purine analog. Patients with resistant relapse are less likely to benefit (response rate, 18%) and should be considered for more intensive intervention, including high-dose therapy.

Other treatment options Rituximab (Rituxan), an anti-CD20 monoclonal antibody, is effective in Waldenström's macroglobulinemia because the CD20 antigen is usually present on the lymphoid cell component of macroglobulinemia. Preliminary results indicate that about 30% of previously treated patients (refractory or relapsing off therapy) may benefit from rituximab.

Striking activity of thalidomide in multiple myeloma has prompted its use in Waldenström's macroglobulinemia. In a series of 20 patients receiving thalidomide, 25% achieved a 50% reduction in paraprotein. Higher doses of

thalidomide were not well tolerated in an elderly cohort of patients.

High-dose therapy with autologous bone marrow or blood stem cell rescue has been effective in achieving 50% reduction in paraprotein in almost all patients in small pilot trials.

Amyloidosis

Amyloidosis occurs in 10% of patients with multiple myeloma. This infiltrative process results from organ deposition of amyloid fibrils, which consist of the NH_2 terminal amino acid residues of the variable portion of the light-chain immunoglobulin molecule. The abnormal protein is produced by clonal plasma cells.

Clinical features include the nephrotic syndrome, cardiomyopathy, hepatomegaly, neuropathy, macroglossia, carpal tunnel syndrome, and periorbital purpura.

Laboratory features Serum and urine immunofixation studies show a monoclonal immunoglobulin in approximately 80% of patients. The light chain is more frequently of the λ than κ type. Diagnosis can be made by the presence of apple-green birefringence on polarized light examination of subcutaneous fat aspirates stained with Congo red.

Treatment of AL (monoclonal protein associated) amyloid Survival of patients with amyloidosis is variable. Patients with congestive heart failure have a median survival of only 4 months. Melphalan and prednisone (given orally) extend the median survival to 17 months, compared with 13 months in untreated patients. Complete hematologic response is rare; similarly, reversal of organ damage is uncommon. In a large cohort of patients receiving high-dose melphalan with stem cell support, a complete hematologic response was observed in 47% of patients with at least 1 year of follow-up. However, the transplant-related mortality is high with high-dose therapy (14%-37%). Complete hematologic response was associated with improved clinical response (improved organ function) and survival. Complete hematologic response in the absence of cardiac involvement predicted excellent outcome (1-year survival, 91%).

Patients with the overlap syndrome of myeloma and AL amyloid should be treated aggressively for myeloma; response can be seen in terms of both myeloma and resolution of amyloid symptoms.

POEMS syndrome

Clinical features and course The POEMS syndrome is a rare plasma cell dyscrasia that presents with peripheral, usually sensorimotor, neuropathy, monoclonal gammopathy (IgA λ being more common), sclerotic bone lesions, noted in nearly all patients, with organomegaly, endocrinopathy, and skin changes.

Other features include hyperpigmentation, hypertrichosis, thickened skin, papilledema, lymphadenopathy, peripheral edema, hepatomegaly, splenomegaly, and hypothyroidism. Diabetes mellitus is not part of this syndrome.

Compared with patients with symptomatic myeloma, individuals with the POEMS syndrome are younger (median age, 51 years) and live longer (median, 8 years). The clinical course is commonly characterized by progressive neuropathy.

Treatment Plasmapheresis does not appear to be of benefit, and patients are often treated similarly to those with myeloma. Patients presenting with isolated sclerotic lesions can have substantial resolution of neuropathic symptoms after local therapy for plasmacytoma with surgery and/or radiotherapy.

Heavy-chain diseases

Heavy-chain diseases are plasma cell dyscrasias characterized by the production of heavy-chain immunoglobulin molecules (IgG, IgA, IgM) that lack light chains.

α Heavy-chain disease results from lymphocyte and plasma cell infiltration of the mesenteric nodes and small bowel and has features of malabsorption, such as diarrhea, weight loss, abdominal pain, edema, and nail clubbing. The heavy-chain molecule may be detected in serum, jejunal secretions, and urine.

γ Heavy-chain disease Patients with γ heavy-chain disease may present with fever, weakness, lymphadenopathy, hepatosplenomegaly, and involvement of Waldeyer's ring. Eosinophilia, leukopenia, and thrombocytopenia are common. Treatment with regimens similar to those used for non-Hodgkin's lymphoma may be effective.

μ Heavy-chain disease is seen exclusively in patients with chronic lymphocytic leukemia (CLL). Vacuolated plasma cells are common in the marrow, and many patients have κ light chains in the urine. Therapy is similar to that used for CLL (see chapter 34).

SUGGESTED READING

ON MULTIPLE MYELOMA

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